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Immunomodulatory Effects of Acupuncture in the Treatment of Allergic Asthma: A Randomized Controlled Study

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ABSTRACT

Objective: According to Traditional Chinese Medicine (TCM) acupuncture is a suitable treatment for complex chronic diseases such as bronchial asthma. In a randomized, controlled study we investigated immunologic effects of Chinese acupuncture on patients with allergic asthma.

Patients and Methods: The effects of acupuncture treatment given according to the principles of TCM (TCM group, $n = 20$) were compared with those of acupuncture treatment using points not specific for asthma (control group, $n = 18$). All patients were treated 12 times for 30 minutes over a time period of 4 weeks. Patients' general well-being and several peripheral blood parameters (eosinophils, lymphocyte subpopulations, cytokines, *in vitro* lymphocyte proliferation) were determined before and after acupuncture treatment.

Results: In the TCM group, significantly more patients indicated an improvement in general well-being (79% in the TCM group versus 47% in the control group; $p = 0.049$) after acupuncture treatment. The following changes were found in the TCM group: within the lymphocyte subpopulations the $CD3^+$ cells ($p = 0.005$) and $CD4^+$ cells ($p = 0.014$) increased significantly. There were also significant changes in cytokine concentrations: interleukin (IL)-6 ($p = 0.026$) and IL-10 ($p = 0.001$) decreased whereas IL-8 ($p = 0.050$) rose significantly. Additionally, the *in vitro* lymphocyte proliferation rate increased significantly ($p = 0.035$) while the number of eosinophils decreased from 4.4% to 3.3% after acupuncture ($p > 0.05$). The control group, however, showed no significant changes apart from an increase in the $CD4^+$ cells ($p = 0.012$).

Conclusion: The results imply that asthma patients benefit from acupuncture treatment given in addition to conventional therapy. Furthermore, acupuncture performed in accordance with the principles of TCM showed significant immune-modulating effects.

INTRODUCTION

With a worldwide increasing prevalence, asthma represents a major and costly health problem. Direct and indirect costs by the disease of asthma add up to 1%–2% of the budget of the health system in Germany (Randerath et al., 1999). Therefore, new therapeutic approaches and treatment strategies are urgently needed.

In the Western world there has been considerable interest in acupuncture as a possible complementary treatment for bronchial asthma. The literature to date provides evidence that acupuncture used in addition to conventional drug therapy in the treatment of patients with

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bronchial asthma may have beneficial effects (Kleijnen et al., 1991). Improvements in general well-being, lung function, as well as a reduction in medication after acupuncture treatment were described (Tashkin et al., 1977; Christensen et al., 1984; Jobst et al., 1986). On the other hand, no statistical significance was found in a Cochrane review of seven controlled trials comparing acupuncture to sham acupuncture (Linde et al., 1999). However, the authors comment that in a number of studies, real acupuncture points indicated for the treatment of asthma according to TCM were used as placebo control. That means that in some studies, two treatments have been compared rather than a treatment and an inert control. A meta-analysis considering this problem yielded 14 of 16 studies in which the combined effect of all acupuncture (i.e., real and sham acupuncture) led to significant improvements (Jobst 1995, 1996).

Previously conducted clinical trials focused mainly on subjective parameters and pulmonary function tests, while immunologic parameters have not been examined. Until now there have been only some experimental studies and a few clinical trials investigating the effects of acupuncture on the immune system in diseases other than asthma. There is some evidence that acupuncture may influence cellular as well as humoral immune responses (Liu et al., 1995; Sato et al., 1996). Increased lymphocyte subgroups, mainly $CD3^+$ and $CD4^+$ cells, and decreased levels of soluble interleukin (IL)-2 receptor after acupuncture have been found in carcinoma patients (Li et al., 1991; Wu, 1995). Furthermore, increases in plaque-forming cells in the blood of mice and enhanced mitogen-induced T-lymphocyte proliferation rates in the blood of rabbits have been observed after acupuncture (Zhao and Liu 1988; Lundeberg et al., 1991).

Allergic asthma is based on a disordered immune response with $CD4^+$ lymphocytes in a leading role. After antigen presentation $CD4^+$ cells differentiate to T_h2-cells, which are characterized by the production of IL-4, IL-5, IL-6, and IL-10. These T_h2-specific cytokines cause various changes during an allergic reaction such as an increasing production of immunoglobulin E (IgE) and a decreasing apoptosis of eosinophils (Kapsenberg et al., 1991; Bochner et al., 1994).

In this study, we sought to investigate the effects of acupuncture treatment applied in addition to conventional therapy by assessing the patients' general well-being as well as several immunological parameters before and after treatment.

PATIENTS AND METHODS

Patients

This was a single-blind, randomized, controlled clinical trial conducted from April 1994 through September 1994 in the Department of Anaesthetics at the University of Heidelberg. Patients were recruited from two pulmonologic practices and via newspaper advertisements. Included were patients with mild to moderately severe bronchial allergic asthma as defined by the *Deutsche Atemwegsliga* 1993 with a minimum of one positive reaction in the prick test, perennial symptoms and any regular antiasthma medication. Further inclusion criteria were a minimum duration of disease of 1 year and a maximum of 20 years. Patients with any other serious diseases or any other therapy (including psychotherapy) were excluded. Furthermore, patients were excluded if they had oral steroids in a dosage higher than 7.5 mg of prednisone daily. The study was passed by the Ethics Committee of Heidelberg University and patients took part with the consent of their general practitioner. All patients gave written informed consent. Patients were free to withdraw from the study at any time.

Treatment

Patients fulfilling all criteria for the study were included. In an initial screening, the lung function was tested and all patients were seen by Dr. H. Zou, an experienced acupuncturist from China working for the Department of Anesthetics at Heidelberg University, for a complete Chinese diagnosis including pulse and tongue diagnosis. All patients were reevaluated after six acupuncture sessions and, if necessary, treatment schedules were changed. Acupuncture treatments were performed on a single-blind basis telling the patient that two different forms of acupuncture were applied.

Acupuncture treatments were performed by six medical students with some basic knowledge of Traditional Chinese Medicine (TCM). They were trained by Dr. Zou for 6 months in acupuncture needling technique to achieve a comparable qualification. All patients received 12 acupuncture sessions of 30 minutes over a period of 4 weeks. In each group, maximally 16 needles (Asia-med GmbH, Munich, Germany) were inserted per patient.

In the TCM group, the patients got an acupuncture treatment consisting of basic points being the same for every patient (BL 13, BL 17, LI 4, and LU 7) and flexible points, which were variable added in accordance to the Chinese diagnosis (e.g., LU 5, LU 6, ST 36, ST 40, KI 3, KI 7, SP 6, SP 9, CV 6, CV 12, or HT 7). The needle depth was between 0.3 and 3 cm depending on the site of insertion and constitution of the patient. At the beginning and at the end of every treatment all needles were manipulated to induce the sensation of *de qi*.

In the control group, patients underwent a treatment at acupuncture points not specific for asthma selected by Dr. Zou. The treatment plan consisted also of basic points (TE 3, TE 19, GB 8, GB 34) and flexible points that were randomly added (BL 38, BL 55, ST 4, ST 6, ST 32, TE 14, TE 23, SI 5). To avoid cuti-visceral reflexes, none of the latter were sited on the trunk. The needle depth was more superficial than in the control group (<1 cm) and the needles were not manipulated.

Patients were required to continue taking their antiasthma medicine, but they were allowed to change the dosage. Changes had to be documented in a diary.

Outcome parameters

Immunologic parameters. Immunologic parameters were determined by the Institute of Immunology at the University of Heidelberg. Three days before the first and 3 days after the last acupuncture treatment, the following immunologic parameters were determined in the peripheral blood: Eosinophils were counted using automatic blood count analysis; Lymphocyte subpopulations were determined by specific binding of monoclonal antibodies to the following subsets analyzed by flow cytometry using standard methods: pan-T lymphocytes ($CD3^+$), T-helper/inducer cells ($CD4^+$), T suppressor/cytotoxic cells ($CD8^+$), activated T lymphocytes ($CD25^+$), B-cells ($CD19^+$), natural killer (NK) cells ($CD16^+$).

Cytokine concentrations were determined using enzyme-linked immunosorbent assay (ELISA) in accordance with standard methods (IL-2, IL-4, IL-6, IL-8: Quantikine kit [Biermann, Bad Nauheim, Germany]; IL-10: Cytoscreen kit [Laboserv, Gießen, Germany]).

In vitro lymphocyte proliferation was determined as relative responses in mixed lymphocyte cultures of patient lymphocytes and pooled allogenic stimulator cells. Stimulation of patient lymphocytes was compared to the stimulation of control cells tested in parallel and relative responses were calculated. Relative responses of less than 0.66 of the responses of the control cells were considered to be reduced.

General well-being. At the end of the treatment period, patients were asked to state whether they had an improvement, a worsening, or no change at all in general well-being. The patients' ratings of response were documented.

Statistical methods

Randomization. Patients were stratified with respect to their age and duration of disease. Randomization was done by numbered envelopes in groups of 6 to 10 patients by the Institute of Biometrics, University of Heidelberg.

Statistical analysis. Statistical processing was performed using PC's STATISTICA. All data are presented as means with the standard error of mean (SEM). Analysis was performed on a per-protocol basis. For comparing the proportions of patients with improved general well-being in the different groups the Fisher exact test was used. To assess differences in baseline and posttreatment measurements, the immunologic parameters were analysed using the Wilcoxon signed rank test. For comparing the efficacy of the treatment between both groups the Mann-Whitney U test was used. p Values of less than 0.05 were regarded as statistically significant. Missing item scores were not replaced.

TABLE 1. BASELINE CHARACTERISTICS ON STUDY ENTRY

	*Baseline characteristics**	
	TCM group	*Control group*
Number of patients: female (n)	13	14
male (n)	7	4
Age (years; range 16–65 years)	35.6	37.9
Duration of disease (years; range: 1–20 years)	10.5	12.1
FEV_1 (%)	72 (±5.9)	74 (±2.5)

*Data given as mean (±SEM).

TCM, Traditional Chinese Medicine; FEV_1, forced expiratory volume in the first second.

RESULTS

A total of 38 patients were randomized and treated. Twenty patients were randomly assigned to the TCM group and 18 patients to the control group. All patients completed the treatment phase. Two patients were excluded from data analysis: one control patient because she became pregnant and one TCM patient because of missing immunologic data. Therefore, 36 patients were included in the per-protocol analysis. Baseline characteristics at the beginning of the study showed no significant differences between the TCM and the control group (Table 1).

General well-being

Fifteen patients (79%) from the TCM group and 8 patients (47%) from the control group stated that they felt an improvement after acupuncture. Four patients (21%) from the TCM group stated that there was no change in their general well-being compared to 9 patients (53%) receiving the control treatment. No patient indicated a decline of general well-being. Analysis with the Fisher exact test demonstrated a significant difference ($p = 0.049$) between both groups (Table 2).

TABLE 2. GENERAL WELL-BEING AFTER ACUPUNCTURE TREATMENT

	*General well-being**	
	Improvement	*No improvement*
TCM group (*n*)	15 (79%)	4 (21%)
Control group (*n*)	8 (47%0	9 (53%)

*Patients rating of response

TCM, Traditional Chinese Medicine.

Immunologic parameters

Except for a slight increase in the number of eosinophils and NK cells, baseline parameters were all within normal limits. Data before and after acupuncture treatment are shown in Table 3. Percentages of baseline scores for selected parameters are given in Figure 1 and 2. The following changes were found in the TCM group: lymphocyte subpopulations $CD3^+$ cells significantly increased by 16% from 1,592 (91) to 1,838 (106) cells per microliter ($p = 0.005$) and $CD4^+$ cells increased by 14% from 1,013 (73) to 1,150 (76) cells per microliter ($p = 0.011$). $CD8^+$, $CD25^+$, and B cells showed smaller, nonsignificant increases. Only the subpopulation of the NK cells decreased, returning to normal after treatment. We also observed several significant changes in cytokine levels in the TCM group: IL-6 ($p = 0.026$) and IL-10 ($p = 0.002$) concentrations decreased while IL-8 concentrations ($p = 0.050$) increased significantly after acupuncture treatment. IL-2 and IL-4 were slightly reduced after acupuncture. The *in vitro* lymphocyte proliferation rate in the TCM group increased significantly 83% ($p = 0.035$). Furthermore, in the TCM group, the eosinophils decreased by 25% from 4.4% (0.9) to 3.3% (0.7) within normal limits. After acupuncture only one patient showed an increase in eosinophils in comparison to seven patients before treatment.

In the control group only the $CD4^+$ lymphocytes showed a significant change after acupuncture treatment. These cells rose by 22% from 943 (68) to 1,147 (70) cells per microliter ($p = 0.013$). There were no significant changes in cytokine concentrations or *in vitro* lympho-

TABLE 3. BASELINE AND POSTTREATMENT MEASUREMENTS OF THE IMMUNOLOGIC PARAMETERS

	TCM group		*Control group*	
	Before acupuncture	*After acupuncture*	*Before acupuncture*	*After acupuncture*
Eosinophils (%)	4.4 (± 0.9)	3.3 (± 0.7)	4.1 (± 0.8)	3.3 (± 0.6)
Panlymphocytes (/μL)	2276 (± 141)	2487 (± 129)	2137 (± 163)	2284 (± 146)
$CD3^+$ cells (/μL)	1592 (± 91)	1838 (± 106)**	1611 (± 126)	1757 (± 112)
$CD4^+$ cells (/μL)	1013 (± 73)	1150 (± 76)*	943 (± 68)	1147 (± 70)*
$CD8^+$ cells (/μL)	701 (± 52)	747 (± 45)	690 (± 80)	671 (± 68)
B-cells (/μL)	181 (± 25)	213 (± 22)	199 (± 21)	221 (± 23)
NK-cells (/μL)	308 (± 43)	290 (± 29)	335 (± 41)	274 (± 36)
$CD25^+$ cells (/μL)	167 (± 25)	179 (± 21)	173 (± 28)	176 (± 22)
IL-2 (pg/mL)	35 (± 15.0)	25 (± 2.3)	33 (± 11.4)	43 (± 17.0)
IL-4 (pg/mL)	24 (± 6.6)	18 (± 4.1)	20 (± 2.4)	18 (± 3.1)
IL-6 (pg/mL)	2 (± 0.4)	1 (± 0.3)*	4 (± 2.3)	1 (± 0.3)
IL-8 (pg/mL)	65 (± 8.4)	104 (± 20)*	93 (± 12.0)	102 (± 9.3)
IL-10 (pg/mL)	7 (± 2.5)	1 (± 0.6)**	4 (± 1.0)	5 (± 3.8)
In vitro proliferation rate	0.81 (± 0.08)	1.48 (± 0.29)*	1.39 (± 0.36)	0.81 (± 0.11)

*$p < 0.05$ = significant. **$p < 0.05$ = highly significant; data given as mean (± SEM)
NK cells, natural killer cells; IL, interleukin; TCM, Traditional Chinese Medicine.

cyte proliferation rate. The statistical comparison between the groups revealed a significantly higher increase of the *in vitro* lymphocyte proliferation rate ($p = 0.010$) in the TCM group. For the remaining immunologic parameters, no significant differences between the two groups were found.

Side effects of the acupuncture treatment were mild. In two cases a syncopal event occurred during acupuncture. Both patients were part of the TCM group. The patients recovered quickly after the acupuncture needles were removed.

DISCUSSION

Acupuncture is a popular and highly appreciated therapy for bronchial asthma in the People's Republic of China. To our knowledge this is the first clinical study investigating immunologic parameters in asthma patients treated with acupuncture.

Altogether our results show that asthma patients benefit from an acupuncture treatment given in addition to conventional therapy. In both treatment groups, general well-being improved after acupuncture. In the TCM group, significantly more patients indicated an improvement than did the control group, which is in good agreement with prior studies (Jobst et al., 1986). However, in our study, a bias in favor of the TCM group cannot be excluded because general well-being was assessed by the therapists themselves.

Furthermore, acupuncture performed in accordance with the principles of TCM was followed by significant changes in several immunologic parameters. In good agreement with prior studies, we observed significant increases in $CD3^+$ and $CD4^+$ cells (Li et al., 1991; Wu, 1995) as well as enhanced *in vitro* lymphocyte proliferation rates in our patients

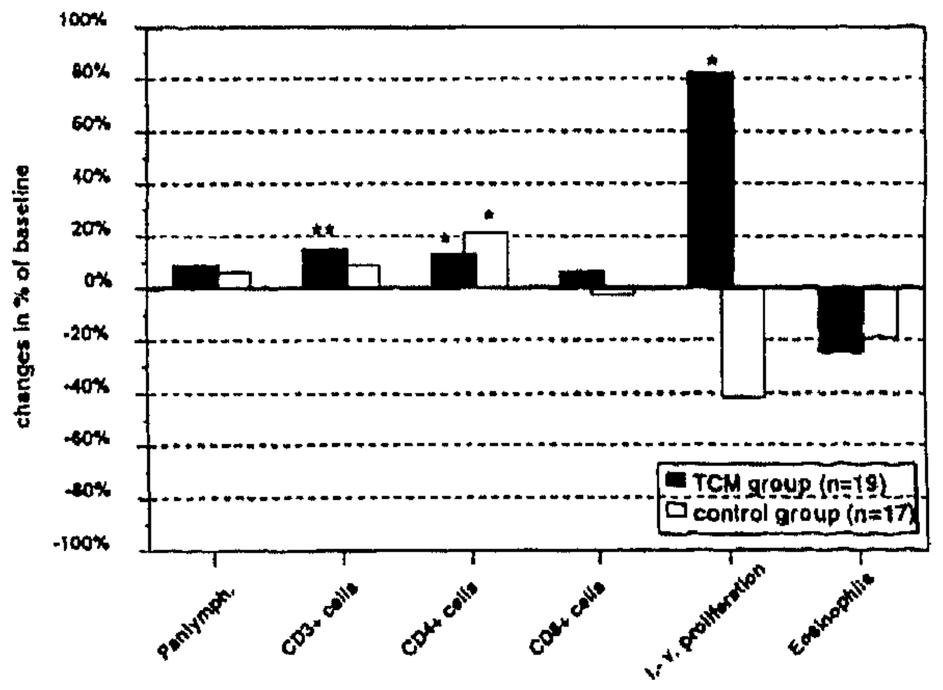

FIG. 1. Changes in lymphocyte subsets, *in vitro* proliferation rate, and eosinophils. *$p < 0.05$ for the difference between baseline and posttreatment measurement; **$p < 0.01$ for the difference between baseline and posttreatment measurement.

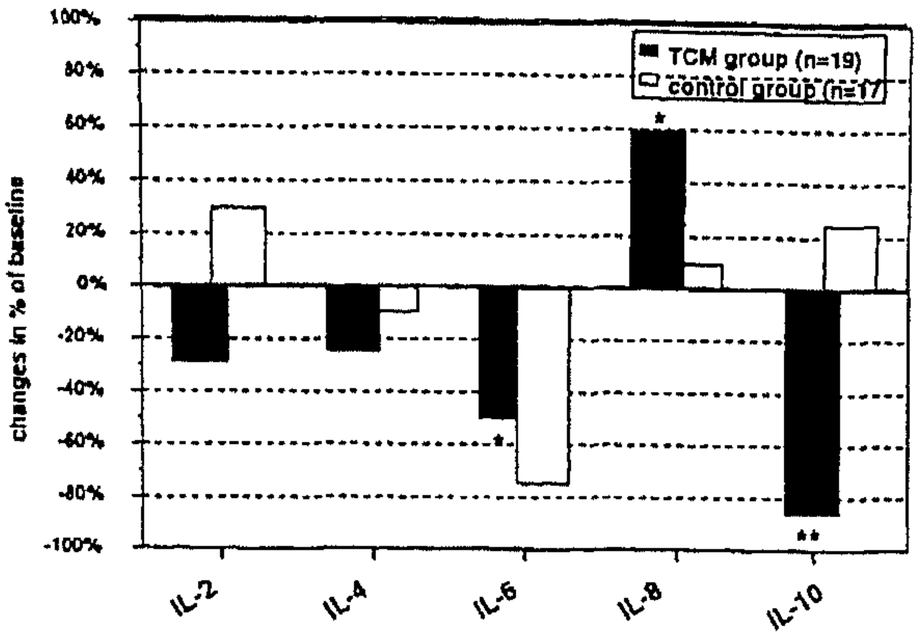

FIG. 2. Changes in cytokine serum levels after acupuncture. $^{*}p < 0.05$ for the difference between baseline and posttreatment measurement; $^{**}p < 0.01$ for the difference between baseline and posttreatment measurement.

(Zhao and Liu 1988; Bianchi et al., 1991). Additionally, we found reduced concentrations of IL-4, IL-6, and IL-10 after acupuncture. A reduction of these T_h2-specific cytokines may indicate an improvement in the immune system of a patient with allergic asthma because these cytokines produce numerous effector mechanisms in the pathogenesis of allergic asthma (Corrigan and Kay, 1992; Bochner et al., 1994). So, the increase in the lymphocyte subsets and in the *in vitro* proliferation rates as well as the decrease in the number of eosinophils seen in our patients can be explained by reduced levels of these T_h2-specific cytokines.

The mechanism of how acupuncture modulates the immune system is still unknown. A possible key role in mediating acupuncture effects is played by the autonomic nervous system. This has been demonstrated in experimental studies in which acupuncture effects were inhibited by β-blockers (Zhao and Liu, 1988; Lundeberg et al., 1991). Furthermore, experimental acupuncture studies also revealed that hormonal factors (corticotropin, β-endorphins, substance P, etc.) are involved in mediating the effects of acupuncture (Kasahara et al., 1993; Jin et al., 1996; Dawidson et al., 1998). Recirculation and proliferation of lymphocytes are modulated both by autonomic fibers via the locus coeruleus and by fibers containing corticotropin-releasing hormone (CRH) (Ottaway and Husband, 1994). It is therefore possible that the immunologic effects observed in our study were mediated through these neuroendocrinal pathways.

Compliance in both groups was good, making it likely that the control treatment was reasonably effective in preserving the blinding although the credibility of the control acupuncture has not been tested in this study. This would have been interesting concerning the much discussed question of what constitutes an acceptable acupuncture control in randomized clinical trials (Vincent and Lewith, 1995; Hammerschlag, 1998). On the one hand, the control procedure should be indistinguishable from the real treatment, which means penetration of the skin is necessary to produce pain sensation. On the other hand, the placebo has to be physiologically inert otherwise it is called sham control (Jobst, 1996). However, any needling or manipulation of the skin is believed to produce a physiologic response. Keeping these much discussed considerations in mind, it can be concluded that there is no acceptable placebo for acupuncture research. This includes the newly developed placebo needle as well (Streitberger et al., 1998). As a result, for controlled acupuncture studies there are two possibilities. Either we use a control treatment distinguishable from the real acupuncture (i.e., transelectrical nerve stimulation [TENS], laser) where we cannot be sure whether we observe a specific acupuncture effect or not. Conversely, when choosing a sham control (i.e., needling wrong points or off-meridian locations), we have to reconsider the physiologic response of the intervention. Assuming the response effects are similar to the hypothetic acupuncture effect, we have to assume that the difference between control and treatment effects will be smaller than if we use a pure placebo. Therefore, achieving significant differences between TCM and control treatment group requires a large number of patients (Lewith and Machin, 1983; Vincent and Richardson, 1986). Although in our study within-patient comparisons in the TCM group show significant changes of several immunologic parameters, after acupuncture significant differences between the groups were not found except for the *in vitro* lymphocyte proliferation rate. The small sample size in our study might be a reason for that.

Nevertheless, our results indicate that acupuncture according to TCM principles in patients with allergic asthma has specific effects on the immune system associated with an im-

provement of general well-being. Further clinical and experimental research is needed to investigate the complexity of the acupuncture effects and to differentiate between specific and nonspecific acupuncture effects.

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